Advances in Drug Design and Development I: NMR Applications

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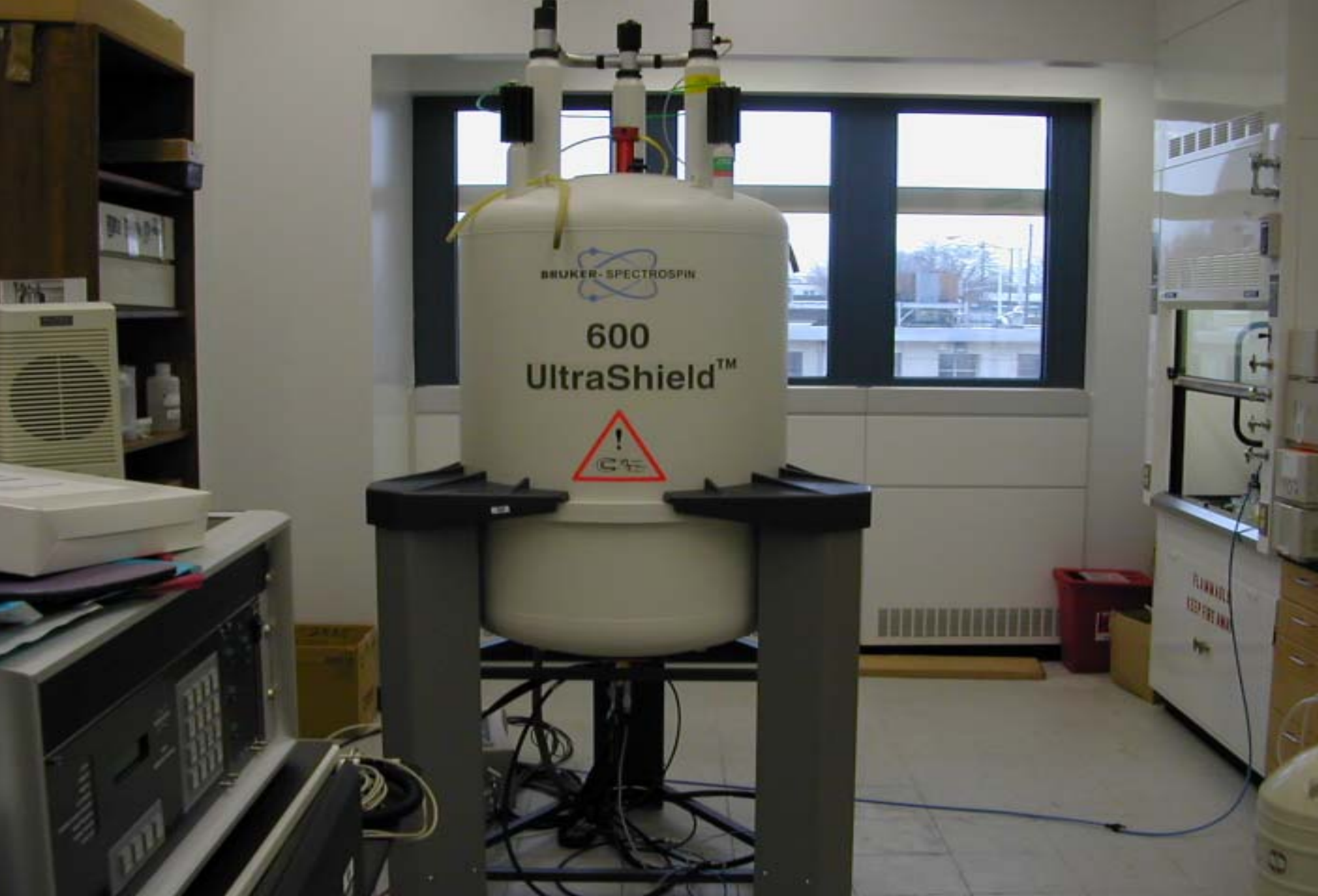
Equipment

- Computer Hardware: five SGI workstations
- Computer Software: InsightII (NMR ADVANCED), Catalyst, Sybyl, Cerius 2, SPARTAN, Gaussian 98
- 600 MHz NMR with cryo-probe
- Peptide synthesizer, combinatorial synthesizer

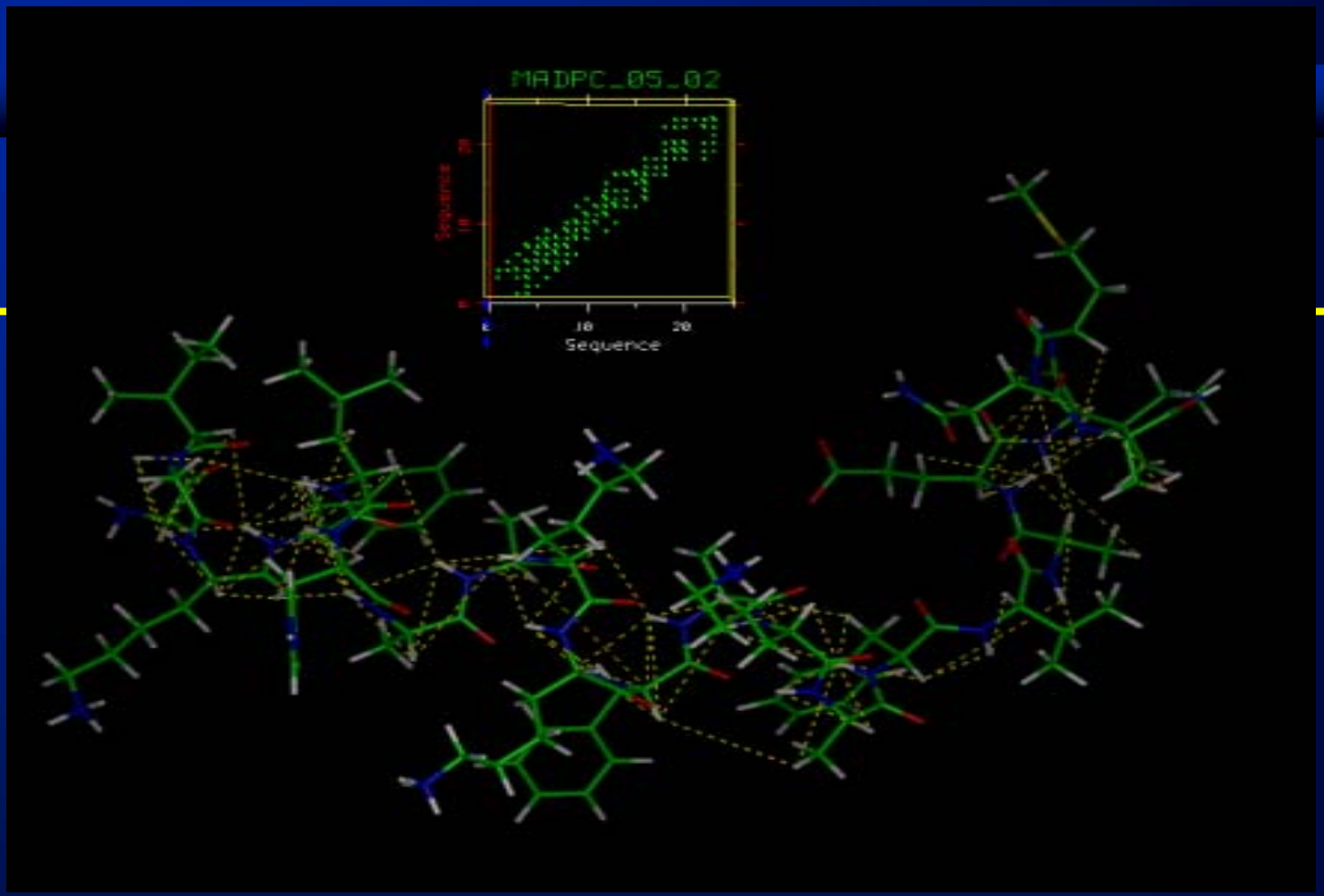

BRUKER-SPECTROSPIN
600
UltraShield™

Fast-Kill Antibacterial Agents 1

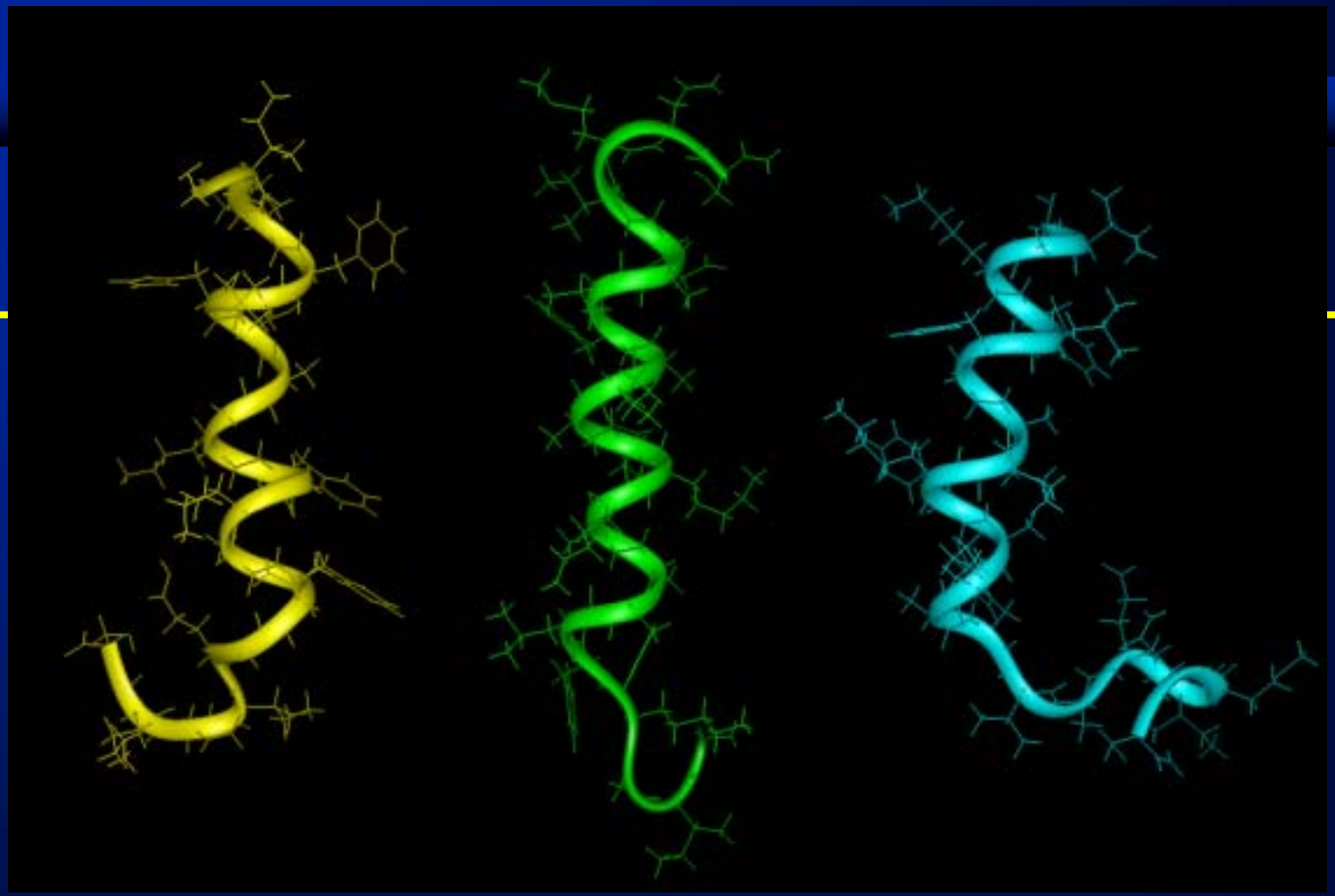
- **Hypothesis: Incorporation of the physicochemical properties of bacteria-selective host defense peptides into an organic skeleton will yield a bacteria-selective "fast-kill" agent for the treatment of severe bacterial infections.**

Fast-Kill Antibacterial Agents 2

- Use NMR to identify the lipid-bound conformation of known host defense peptides.
- Develop a 3D pharmacophore that describes the physicochemical requirements for selective and high antibacterial activity.
- Subsequently design a non-peptide skeleton that will incorporate the essential physicochemical requirements for the desired biological activity.
- Synthesize non-peptide antibacterials.
- For enzymes, would also develop an NMR screening protocol.



NOEs observed in the 2-D NOESY spectrum of (Ala ^{8,13,18})magainin 2 amide bound to DPC micelles. The NOE parameters were employed as inter-proton distance restraints in simulated annealing molecular dynamics calculations to determine the 3-dimensional conformation of the peptide bound to the micelle.



A comparison of the micelle bound conformations of magainin 1 in SDS (yellow) with (Ala ^{8,13,18})magainin 2 amide in SDS (green) and DPC (blue) indicate that all are helical in the mid-region of the peptides with differing degrees of flexibility at the N and C-terminal regions of the peptide.

Summary

- NMR techniques complement X-Ray crystallography since they provide angstrom level detail without the need for a crystal and allows for molecular motion in a solution phase. Also crystallography is very difficult to apply to lipid systems.
- We have used NMR techniques on several systems to determine the three-dimensional structures of peptides bound to lipids and proteins.
- With advanced molecular modeling techniques, this information identifies possible non-peptide chemotherapeutics.